

Claims

1. A process for the preparation of multiple cross-linked derivatives of hyaluronic acid, which process comprises covalently cross-linking HA via two or more different functional groups, wherein said cross-linking is effected by contacting HA with one or more chemical cross-linking agents so as to form two or more chemically distinct cross-links, between said HA molecules
2. A process according to claim 1 wherein the functional groups are selected from hydroxyl, carboxyl and amino.
3. A process according to claim 1 or claim 2 wherein the crosslinking is effected by means of two or more different bonds selected from ether, ester, sulfone, amine, imino and amide bonds.
4. A process according to any of claims 1 to 3 wherein the cross-linking agent is selected from formaldehyde, glutaraldehyde, divinyl sulfone, a polyanhydride, a polyaldehyde, a polyhydric alcohol, carbodiimide, epichlorohydrin, ethylene glycol diglycidylether, butanediol diglycidylether, polyglycerol polyglycidylether, polyethylene glycol diglycidylether, polypropylene glycol diglycidylether, or a bis-or poly-epoxy cross-linker.
5. A process according to any of claims 1 to 4 wherein an ether bond is formed using a crosslinking agent selected from bis and poly epoxides under alkaline conditions.
6. A process according to any of claims 1 to 4 wherein an ester bond is formed using a crosslinking agent selected from bis and poly epoxides under acidic conditions.
7. A process according to claim 5 or claim 6 wherein the crosslinker is selected from 1,2,3,4-diepoxybutane and 1,2,7,8-diepoxyoctane.
8. A process according to any of claims 1 to 4 wherein an ether bond is formed using a glutaraldehyde cross-linking agent under acidic conditions.

Sub 9.
A² cont
9. A process according to any of claims 1 to 8 wherein the crosslinking of each type of functional group is effected sequentially.

10. A process according to claim 9 which comprises cross-linking HA via a first functional group and subsequently further cross-linking the product via a second functional group, wherein said first and second functional groups represent different chemical entities.

Sub 11.
A³
11. A process according to claim 9 or claim 10 wherein HA is first cross-linked via the hydroxyl groups by formation of ether bonds and subsequently cross-linked via the carboxyl groups by formation of ester bonds.

Sub 12.
A⁴
12. A process according to any of claims 1 to 8 wherein the crosslinking of each type of functional group is effected simultaneously.

Sub 13.
A⁵
13. A process according to any of claims 1 to 12 for preparing double crosslinked HA.

14. A process according to claim 13 which comprises:
(a) cross-linking HA via a first functional group and
(b) subsequently further cross-linking the product of (a) via a second functional group, wherein said first and second functional groups represent different chemical entities.

Sub 15.
A⁶
15. Multiple cross-linked HA obtainable by a process according to any of claims 1 to 14.

16. HA cross-linked to a further molecule of HA wherein the HA is crosslinked by at least two different types of bond.

Sub 17.
A⁷
17. Cross-linked HA according to claim 15 or claim 16 wherein the crosslinking bonds are selected from two or more of ether, ester, sulfone, amine, imino and amide bonds.

Sub 18.
A⁸
18. Multiple cross-linked HA according to any of claims 15 to 17 in the form of a film.

Sub 19.
A⁹
19. Multiple cross-linked HA according to any of claims 15 to 17 in the form of a gel.

20. HA according to any of claims 15 to 19 which is double cross linked HA.

21. A product comprising multiple cross-linked HA according to any of claims 15 to 20.

22. The use of HA according to any of claims 15 to 20 in the preparation of a product for pharmaceutical, cosmetic or medical use.

23. The use of HA according to any of claims 15 to 20 or a product according to claim 21 in medicine or surgery.

1944-45	1945-46	1946-47	1947-48	1948-49	1949-50	1950-51	1951-52	1952-53	1953-54	1954-55	1955-56	1956-57	1957-58	1958-59	1959-60	1960-61	1961-62	1962-63	1963-64	1964-65	1965-66	1966-67	1967-68	1968-69	1969-70	1970-71	1971-72	1972-73	1973-74	1974-75	1975-76	1976-77	1977-78	1978-79	1979-80	1980-81	1981-82	1982-83	1983-84	1984-85	1985-86	1986-87	1987-88	1988-89	1989-90	1990-91	1991-92	1992-93	1993-94	1994-95	1995-96	1996-97	1997-98	1998-99	1999-00	2000-01	2001-02	2002-03	2003-04	2004-05	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19	2019-20	2020-21	2021-22	2022-23	2023-24	2024-25	2025-26	2026-27	2027-28	2028-29	2029-30	2030-31	2031-32	2032-33	2033-34	2034-35	2035-36	2036-37	2037-38	2038-39	2039-40	2040-41	2041-42	2042-43	2043-44	2044-45	2045-46	2046-47	2047-48	2048-49	2049-50	2050-51	2051-52	2052-53	2053-54	2054-55	2055-56	2056-57	2057-58	2058-59	2059-60	2060-61	2061-62	2062-63	2063-64	2064-65	2065-66	2066-67	2067-68	2068-69	2069-70	2070-71	2071-72	2072-73	2073-74	2074-75	2075-76	2076-77	2077-78	2078-79	2079-80	2080-81	2081-82	2082-83	2083-84	2084-85	2085-86	2086-87	2087-88	2088-89	2089-90	2090-91	2091-92	2092-93	2093-94	2094-95	2095-96	2096-97	2097-98	2098-99	2099-00	2100-01	2101-02	2102-03	2103-04	2104-05	2105-06	2106-07	2107-08	2108-09	2109-10	2110-11	2111-12	2112-13	2113-14	2114-15	2115-16	2116-17	2117-18	2118-19	2119-20	2120-21	2121-22	2122-23	2123-24	2124-25	2125-26	2126-27	2127-28	2128-29	2129-30	2130-31	2131-32	2132-33	2133-34	2134-35	2135-36	2136-37	2137-38	2138-39	2139-40	2140-41	2141-42	2142-43	2143-44	2144-45	2145-46	2146-47	2147-48	2148-49	2149-50	2150-51	2151-52	2152-53	2153-54	2154-55	2155-56	2156-57	2157-58	2158-59	2159-60	2160-61	2161-62	2162-63	2163-64	2164-65	2165-66	2166-67	2167-68	2168-69	2169-70	2170-71	2171-72	2172-73	2173-74	2174-75	2175-76	2176-77	2177-78	2178-79	2179-80	2180-81	2181-82	2182-83	2183-84	2184-85	2185-86	2186-87	2187-88	2188-89	2189-90	2190-91	2191-92	2192-93	2193-94	2194-95	2195-96	2196-97	2197-98	2198-99	2199-00	2200-01	2201-02	2202-03	2203-04	2204-05	2205-06	2206-07	2207-08	2208-09	2209-10	2210-11	2211-12	2212-13	2213-14	2214-15	2215-16	2216-17	2217-18	2218-19	2219-20	2220-21	2221-22	2222-23	2223-24	2224-25	2225-26	2226-27	2227-28	2228-29	2229-30	2230-31	2231-32	2232-33	2233-34	2234-35	2235-36	2236-37	2237-38	2238-39	2239-40	2240-41	2241-42	2242-43	2243-44	2244-45	2245-46	2246-47	2247-48	2248-49	2249-50	2250-51	2251-52	2252-53	2253-54	2254-55	2255-56	2256-57	2257-58	225
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